

ized technique for the examination. This latter method has great utility in acutely ill patients or in emergency situations. Increased relative size of the right ventricle and abnormal interventricular septum motion are observed in conditions with diastolic volume overload of the right ventricle such as atrial septal defect, anomalous pulmonary venous return and tricuspid regurgitation. End-diastolic and end-systolic left ventricular diameters measured echographically may be used to calculate total left ventricular stroke volume and ejection fraction. If there is valvular regurgitation, the difference between total ventricular stroke volume and effective or forward stroke volume measured by the Fick method gives a quantitative estimate of the degree of regurgitation. Also, echographically determined velocity of left ventricular epicardial motion has been used as an index of ventricular contraction.

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Combination Drug Therapy in Metastatic Carcinoma of the Breast

THE USE OF COMBINATIONS of cytotoxic agents in the treatment of advanced cancer has proved to be superior to single agent therapy in clinical response and survival in leukemia and lymphoma. Recently, encouraging results have been obtained in other metastatic solid tumors.

Metastatic carcinoma of the breast which is unresponsive to or has relapsed from endocrine therapy has recently been shown to be quite responsive to a five-drug combination including 5-fluorouracil, methotrexate, cyclophosphamide, vincristine and prednisone, with good to excellent responses in more than 70 percent of patients. Similar high complete response rates have been obtained with modifications of this therapy in several institutions. We have obtained good to excellent responses in 68 percent of patients treated with 5-fluorouracil, methotrexate and cyclophosphamide. Toxicity from this drug combination has been low.

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Hypothalamic Hypothyroidism

THE SIMULTANEOUS OCCURRENCE of a low thyroid hormone level and a normal or low serum level of thyroid stimulating hormone (TSH) in a patient with hypothyroidism establishes the diagnosis of secondary hypothyroidism. The administration of thyrotropin releasing hormone (TRH), which is normally synthesized and released by the hypothalamus, enables the physician to distinguish between pituitary and hypothalamic causes of hypothyroidism. TRH will normally cause the release of TSH from the pituitary gland. This will occur even in the face of an elevated TSH level in patients with primary hypothyroidism. If the thyrotroph cells of the pituitary gland are destroyed, no rise in TSH occurs. When the hypothalamus does not synthesize or release TRH, the administration of exogenous TRH will result in prompt rise of serum TSH. To date, the cases reported of pituitary hypothyroidism have been associated with pituitary tumors, hypophysectomy or postpartum necrosis of the pituitary gland. Hypothalamic hypothyroidism, on the other hand, may either be idiopathic or result from demonstrable hypothalamic disease, and it accounts for most cases previously attributed to an idiopathic pituitary TSH deficiency. The TRH stimulation test can therefore aid in more accurate localization of certain destructive processes of the central nervous system.

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Indications for Lavage in the Treatment of Bronchopulmonary Disease

SEGMENTAL LUNG LAVAGE has been attempted for many years in the treatment of a variety of pulmonary diseases. In recent years, a technique using "volume-controlled lung lavage" has been reported to be of value in certain circumstances.

With the use of a Carlens tube, one can isolate the two lungs, allowing for ventilation of one lung while lavage is being carried on in the other. Normal saline solution is used as the basic lung irrigant. Monitoring of serial arterial blood gas

samples during the lung lavage is important to insure that an adequate arterial PO_2 is being maintained.

"Volume-controlled lung lavage" has been used in the treatment of pulmonary alveolar proteinosis, chronic bronchitis, cystic fibrosis, bronchial asthma, pneumonia, desquamative interstitial pneumonitis, bronchiectasis, Goodpasture's syndrome, and accidental radioactive particle inhalation.

In alveolar proteinosis, lung lavage consistently results in improvement, and in fact, may be life-saving. Multiple lavages may be required in the treatment of this disorder.

In "status asthmaticus," lack of appropriate response to therapy may be due to diffuse plugging of airways with thick tenacious mucus. Removal of these plugs by lung lavage may greatly improve alveolar ventilation.

In cystic fibrosis, it would be expected that lung lavage would be of great benefit. However, one cannot recommend this as general practice, since experience with lavage in this disease is quite limited.

The clinical experience with lung lavage in the treatment of bronchiectasis, Goodpasture's syndrome, desquamative interstitial pneumonitis, chronic bronchitis, pneumonia, and inhalation of radioactive particles is not large enough to allow one to make recommendations as to the efficacy of this procedure in these disorders.

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Alpha₁-Antitrypsin Deficiency

AN ASSOCIATION between pulmonary emphysema and a deficiency of serum antitrypsin activity was first reported by Swedish investigators in 1963. This discovery has improved our understanding of the pathogenesis of pulmonary emphysema, and has resulted in the ability to detect individuals inherently predisposed to chronic obstructive lung disease. Alpha₁-antitrypsin is the major component of the alpha₁-globulin fraction of human serum, and it is inhibitory to a number of proteolytic enzymes including trypsin, elastase, chymotrypsin, and the leukocytic proteases. Being an acute phase reactant protein, alpha₁-antitrypsin

has a fluctuating level that responds to infection, inflammation, estrogens and acute or chronic destructive tissue processes.

The proteolytic enzymes of leukocytes have been accused of causing the destructive process leading to pulmonary emphysema. In the advent of an intrapulmonary inflammatory reaction, leukocytes and other macrophages invade the area to engulf and digest cellular debris, but the lung parenchyma is protected from the digestive action of macrophagic proteases by the alpha₁-protease inhibitor. Persons with inherited deficiency of alpha₁-antitrypsin are unable to increase their level of antiprotease activity high enough to prevent the digestion of pulmonary alveoli, and emphysema results.

The inheritance pattern for antitrypsin deficiency involves two co-dominant genes. Abnormality of one of the two genes (heterozygosity) results in intermediate levels of antitrypsin activity, whereas the homozygous state results in a severe deficiency of this activity (approximately 10 percent of normal activity). It had originally been thought that only the severe homozygous deficiency state could result in pulmonary emphysema, but more recent findings have raised the very startling possibility that the heterozygous state may also predispose to chronic lung disease. If true, the number of affected persons would approximate 5 percent of the population. If only the homozygous condition predisposed to lung disease, the number of susceptible persons would be much less. Studies to date suggest that a heterozygous person is protected to a degree by his intermediate level of antitrypsin activity, but that continued or recurrent inflammation, as would occur in a heavy cigarette smoker, renders this limited protection inadequate.

The type of lung disease that occurs in these persons appears to be primarily a pure type of emphysema with predilection for the lung bases. This is in contradistinction to emphysema in persons with normal antitrypsin activity, where the upper lung fields seem to be primarily involved. In those with homozygous deficiency of antitrypsin activity, lung disease tends to develop at a younger age than in those with heterozygous antitrypsin deficiency or those with normal antitrypsin activity. It has been reported that a person in whom emphysema develops before age 50 has approximately a 50 percent chance of having either homozygous or heterozygous antitrypsin deficiency.

Current research is dealing with improved